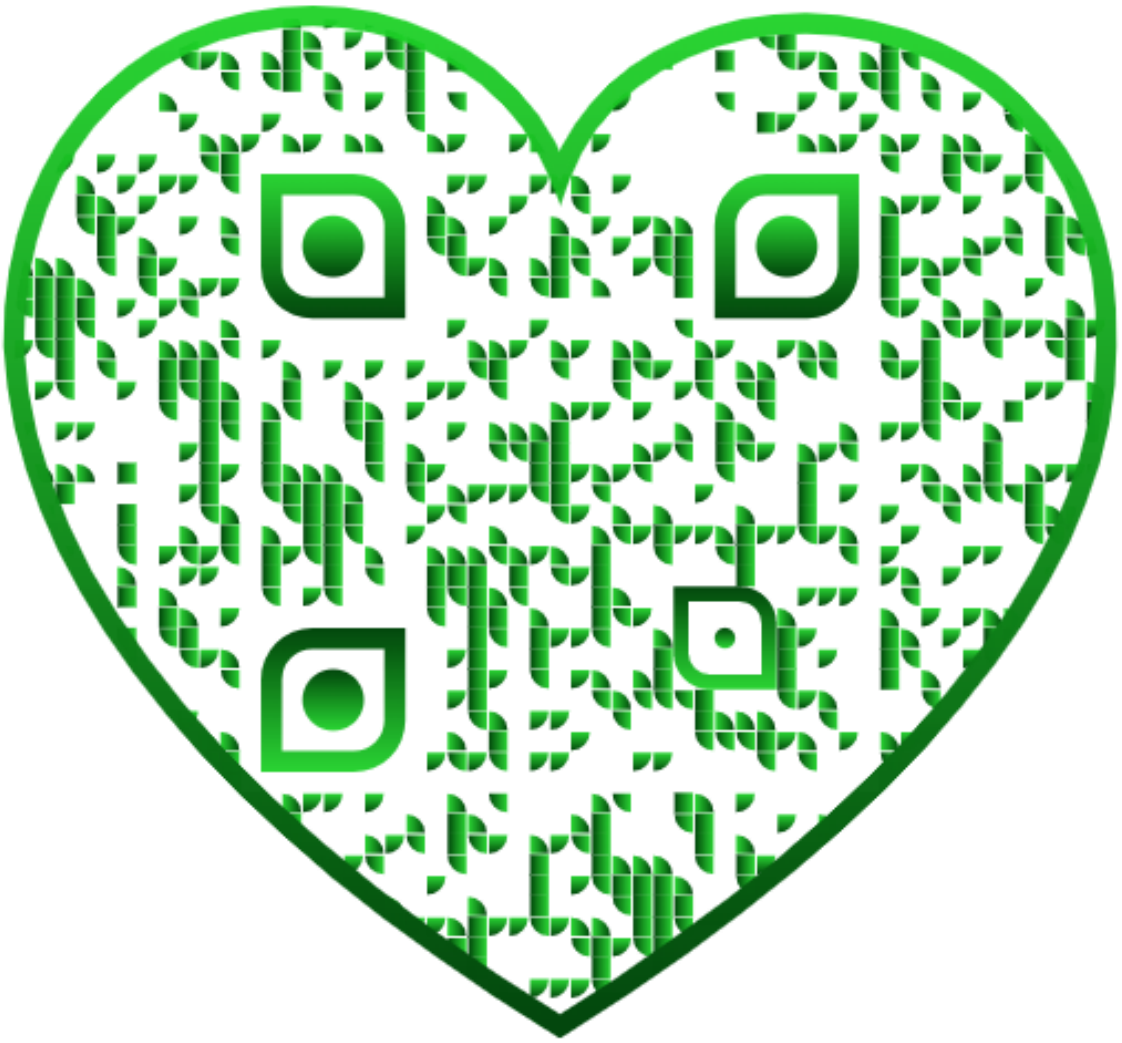
Pharmaceutical Aerosols

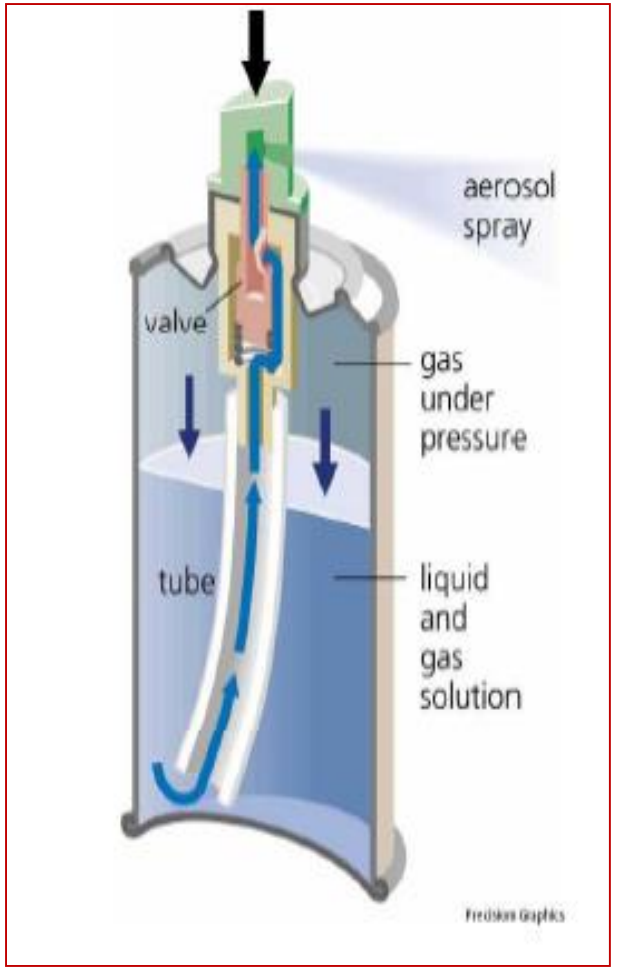


Introduction

- Definitions:
  - A colloidal system containing liquid and solid particles (**API**) suspended in a **propellant** (liquefied gas or compressed gas).
  - Aerosol is a system that depends on the power of a compressed or liquefied gas to expel the contents from the container.
  - When pressure is applied to the valve the contents are expelled out in the form of **mist**, **spray**, **steam** or **foam**
  - Aerosols are meant for topical, systemic, and oral administration.

- History:
  - Aerosol industry begins in 1942, aerosol insecticide developed by good hue and sullivan of the US department of agriculture
  - The principal of aerosol technology were applied to the development of pharmaceutical aerosol in early 1950s
  - In 1950s intended for topical administration
  - In 1955 intended for local activity in the respiratory tract

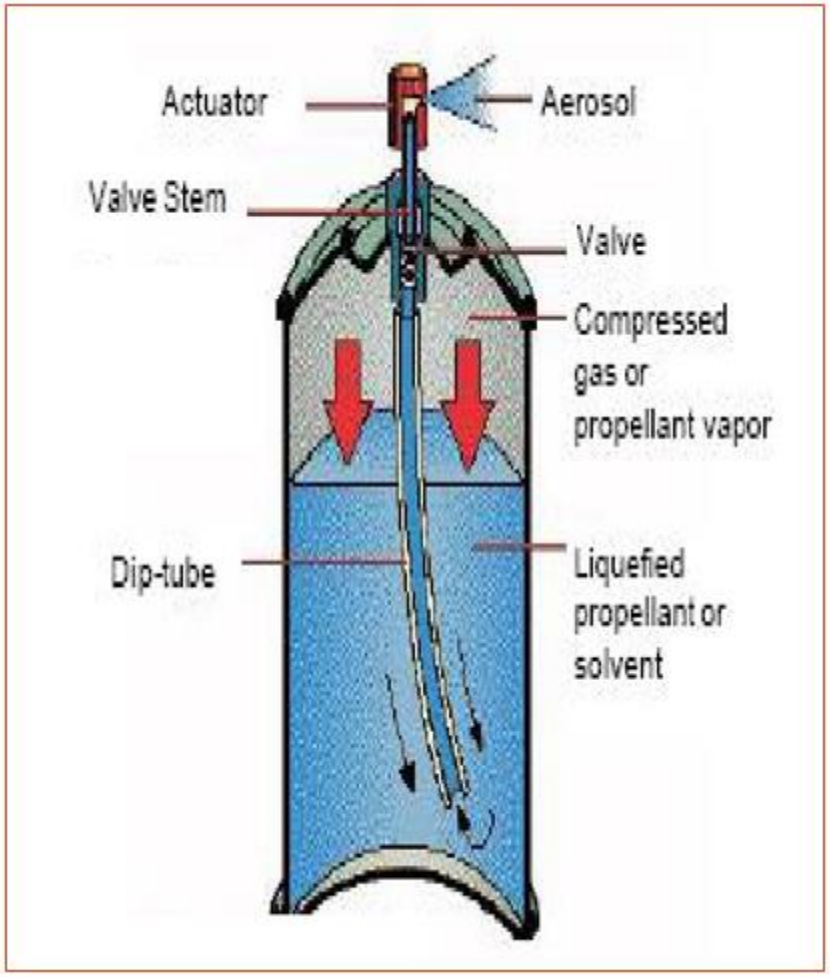
- Operation:
  - Pressure on the **actuator** moves the stem down.
  - This breaks the seal between the gasket and the stem.
  - The stem is exposed to the product/propellant in the container (i.e. the valve is open).
  - Pressure inside the container pushes the product through the valve to the outside of the container.
  - By releasing the actuator, the spring returns the stem orifice to the sealed position (i.e. the valve is closed)



- Advantages:
  - Dose can be removed with out contamination.
  - Medication can be delivered directly to the affected area.
  - Ease and convenience of application.
  - Lower dosage of drug, minimize adverse side effect
  - Onset of effect with inhaled drug is faster than with oral dosing
  - Less painful than IV

- Limitations
  - Expensive
  - Performance of package can deteriorate during life of product
  - Flammable
  - Propellants are toxic in nature

- Components
  - Propellant
  - Container
  - Valve and actuator
  - Product concentrate



Propellant

- It is responsible for developing the vapor pressure within the container.
- Expel the product when the valve is opened and aids in the atomization or foam production of the product.
- It may also act as a solvent of a drug.
- Generally mixture of propellants is used to get a desired vapor pressure and solvent property.

- Ideal characteristics of propellant:
  - Economical,
  - Non toxic, non-irritant,
  - Odorless,
  - Physically and chemically stable,
  - Should dissolve wide range of medicament,
  - Compatible with container, valve system and drug

Types of propellant

LIQUEFIED GAS SYSTEM

- FLUORINATED HYDROCARBON(FHC)
- HYDROCARBONS (HC)
- HYDROFLUOROALKANES (HFA)

COMPRESSED GAS SYSTEM

- **Insoluble in water**
  - Argon
  - Nitrogen
- **Soluble in water**
  - CO_2
  - Ammonia

- FHC ~ for oral and inhalation use
- HC and compressed gas ~ for topical use

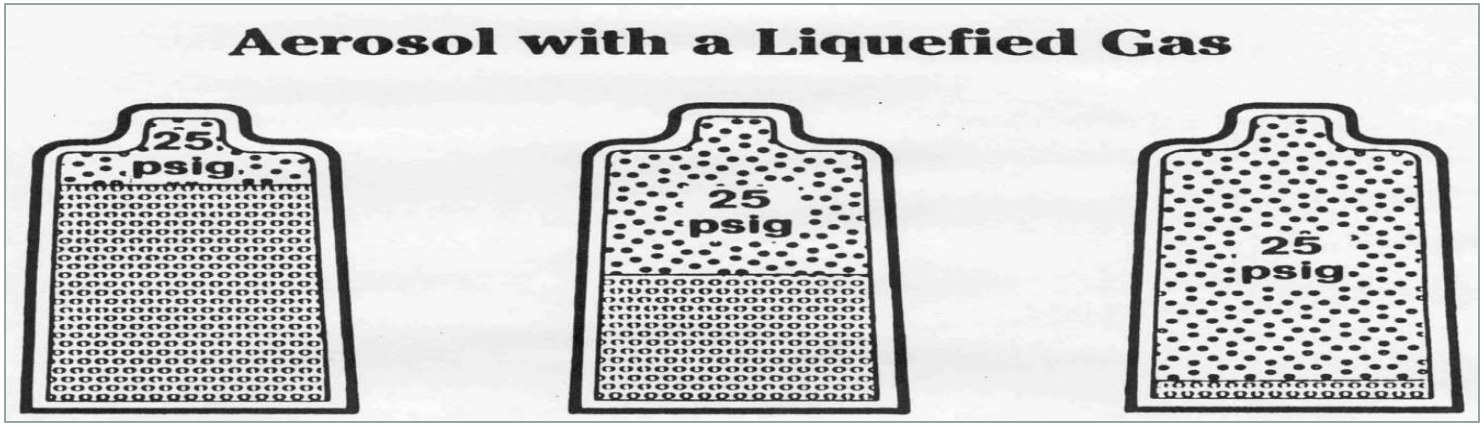
Liquefied Gas Systems

- These compounds are gases at room temperature and atmospheric pressure.
  - However they can be liquefied easily by lowering the temperature (below the boiling point or by increasing pressure).
  - These compounds are chosen generally have boiling point below 21^{o}C and vapor pressure between 14 and 85 psig (pounds per sq. inch gauge) at 21^{o}C.

- When it is placed into sealed container it immediately separates into a liquid and a vapor phase
- Some of the propellant molecule will leave from the liquid state to vapor state.
  - The pressure at this point is called vapor pressure.
- As molecule enter the vapor state a pressure gradually develops
- Because the aerosol is under pressure the propellant exists mainly as a liquid, but it will also be in the head space as a vapor.

- As the product is used up as the valve is opened, some of the liquid propellant turns to vapor and keeps the head space full of vapor.

- In this way the pressure in the can remains constant and the spray performance is maintained throughout the life of the aerosol.



- **Fluorinated Hydrocarbons**
  - For almost all types of pharmaceuticals, inhalation and oral preparations.
  - Advantage
    - Chemical inertness, Lack of toxicity, Non flammability and explosiveness
  - Disadvantage
    - High cost, and it depletes the ozone layer

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It is Used for oral and inhalation aerosol preparation.

Chemical Name	Chemical Formula	Numerical Designation
Trichloromonoflouromethane	CCl_3F	11
Dichlorodifluoromethane	CCl_2F_2	12
Dichlorotetrafluroethane	$CClF_2CClF_2$	114
Chloropentaflouroethane	$CClF_2CF_3$	115
Monochlorodifluroethane	CH_3CClF_2	142[b]
Difluroethane	CH_3CHF_2	152 [b]
Octaflurocyclobutane	$CF_2CF_2CF_2CFM_2$ 12	C318

- **Hydrocarbons**
  - They are lighter than water hence they remain on the top of aqueous layer and serves to push the contents out of container.
  - It is mainly used for the preparation of topical preparations.
  - Advantage
    - Inexpensive, Excellent solvents, Chemically stable, It does not cause ozone depletion.
  - Disadvantage
    - Flammable, and Unknown toxicity produced

Protection of the ozone layer

- In 1987, after the signing of the **Montreal Protocol** (UN Program for the Environment) aerosols no longer contain CFCs.

  Nor do they contain any of the other substances regulated by the revisions of the Montreal Protocol.

- These gases have been replaced by other compressed or liquefied gases which do not harm the ozone layer.

- CFCs contain chlorine which attacks ozone in the upper atmosphere.

- **Hydrofluoroalkanes**
  - Advantages
    - Low inhalation toxicity, High chemical stability, High purity, Not ozone depleting.
  - Disadvantages
    - Poor solvents, Minor “greenhouse effect”, and High cost

Compressed Gas System

- Compressed gas propellants only occupy the head space above the liquid in the can.
- When the aerosol valve is opened the gas 'pushes' the liquid out of the can.
- The amount of gas in the headspace remains the same but it has more space, and as a result the pressure will drop during the life of the can.

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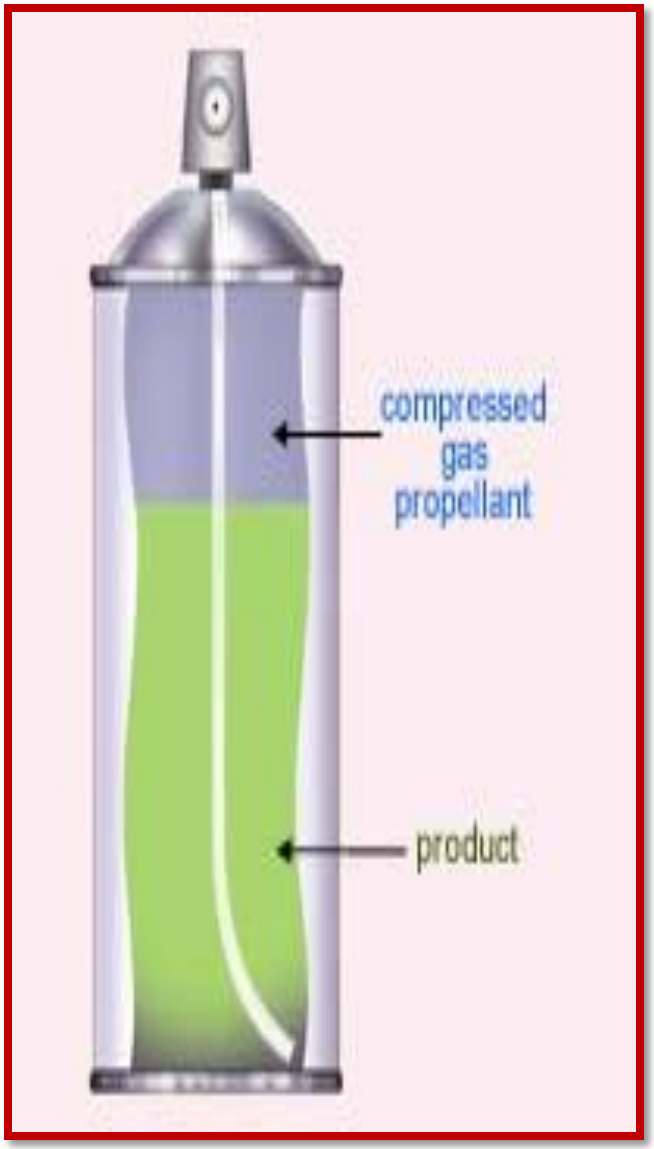
- They have widespread use in aerosols for oral and inhalation use.



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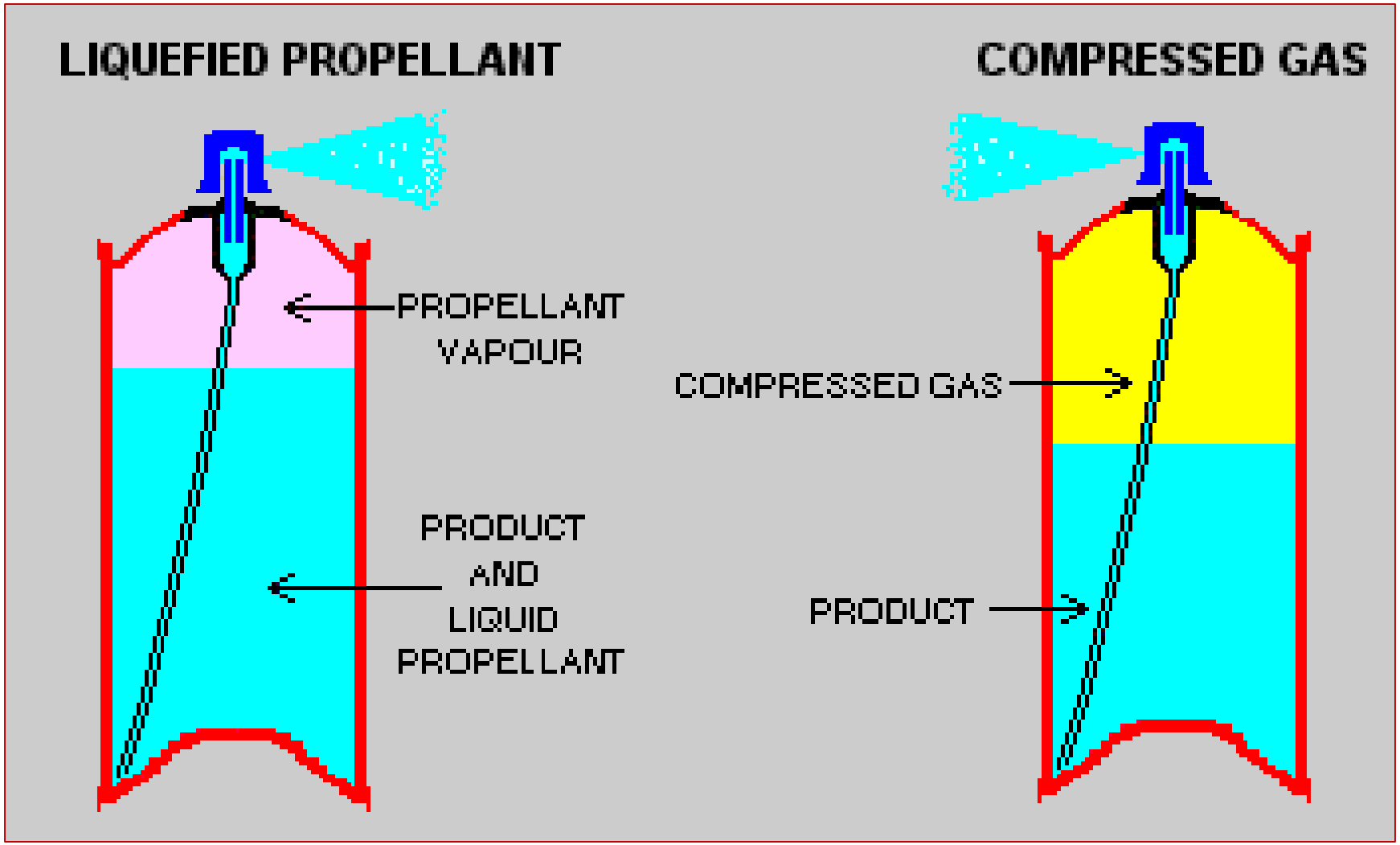
- Advantages
  - Low inhalation toxicity,
  - High chemical stability
  - Inexpensive
  - No environmental problems
- Disadvantages
  - Require use of a nonvolatile co-solvent
  - Produce course droplet sprays
  - Pressure falls during use


LIQUEFIED PROPELLANT
COMPRESSED GAS
PROPELLANT VAPOUR
PRODUCT AND LIQUID PROPELLANT
COMPRESSED GAS
PRODUCT

Aerosol Container

- Containers must withstand pressure as high as 140 to 180 psig.
- Different types of containers are used which are:
  - **Metals**: Tin plated steel, Aluminum, Stainless steel
  - **Glass**: Uncoated glass, Plastic coated glass, Plastic

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- Tin-plate steel:
  - These containers consist of steel plate that has been electroplated on both sides with tin
- Aluminum containers:
  - Less danger of incompatibility.
  - Can be coated with organic materials to provide additional resistance
  - Light weight and not fragile
  - Good for light sensitive drugs

- Stainless steel containers:
  - Limited to small size due to production problems and cost.
  - They are extremely strong and resistant to most materials.
  - In most cases no internal coating is used.

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- Glass container
  - Limited to those products having lower pressure and lower percentage of propellant.
  - Use of glass allows greater degree of freedom in design of container.
  - No corrosion problems
  - Can have various shape because of molding

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- Two types of glasses namely;
  - **Uncoated glass:**
    - Low cost and provide clarity by which all the contents of the container can be viewed.
    - Compatible with many additives.
    - Not for light sensitive drugs.
  - **Plastic coated glass:**
    - Protected by plastic coating that prevents the glass from shattering in the event of breakage.
    - Epoxy or vinyl coating are generally used.

Why a curved bottom aerosol container?

- In most aerosol cans, the bottom curves inward. This serves two functions:

1. The shape strengthens the structure of the can.
    - If the can had a flat bottom, the force of the pressurized gas might push the metal outward.
    - A curved bottom has greater structural integrity.
2. The shape makes it easier to use up all the product.

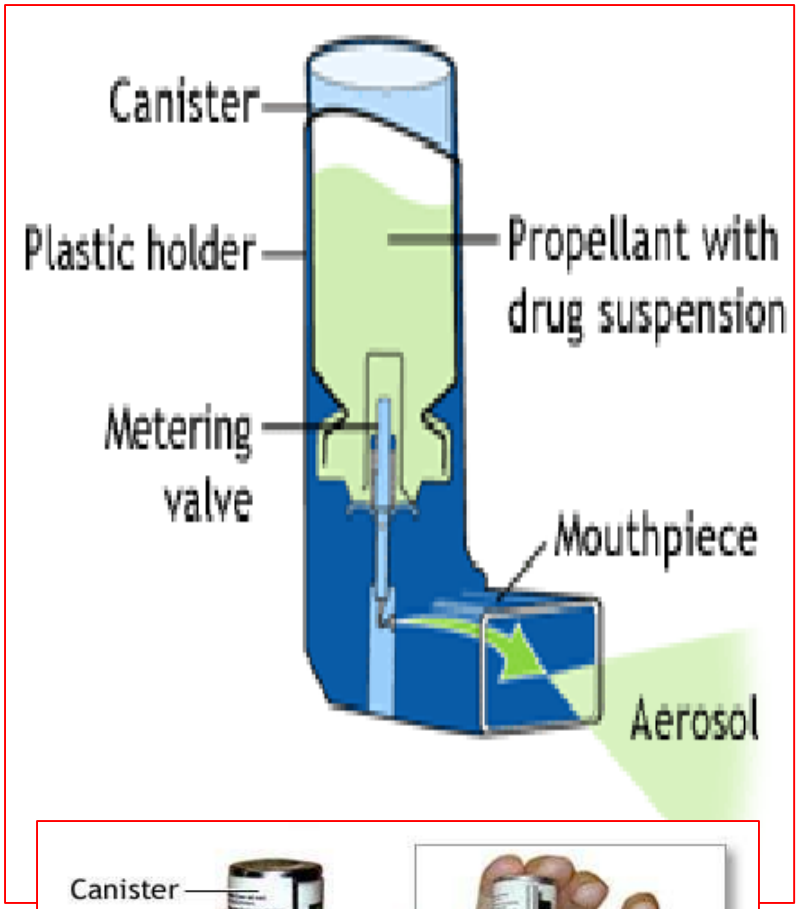
Valves

- Purpose:
  - To deliver the drug in desired form.
  - To give proper amount of medication.
- Types:
  - Continuous spray valve
  - Metering valves

- Continuous spray valve
  - Used for most topical aerosols.
  - Product is released as long as pressure is maintained on the actuator.
- Metering valves
  - Used for all inhalation and some topical aerosols.
  - A finite volume of product is released when the actuator is pressed.
  - No more product is released unless the actuator is returned to its rest position and repressed

Metered dose inhaler

- A pressurized container with metered-dose valve and mouthpiece.
- The exact amount of the drug is expelled in the proper particle size to achieve maximum deposition in the lungs.
- Formulated as solution or suspension.



- Valve components

1. Stem
    - Support the actuator and deliver the formulation in the proper form to the chamber of the actuator.
2. Gasket
    - Prevent the leakage of the formulation when the valve is closed.
3. Spring
    - Hold the gasket in place and when the actuator is depressed and released, the spring will return the valve to its closed position.

4. Mounting cup

- Used to attach the valve to the aerosol container. Since it is exposed to the formulation, it should be manufactured from an inert material to prevent an undesired interaction.

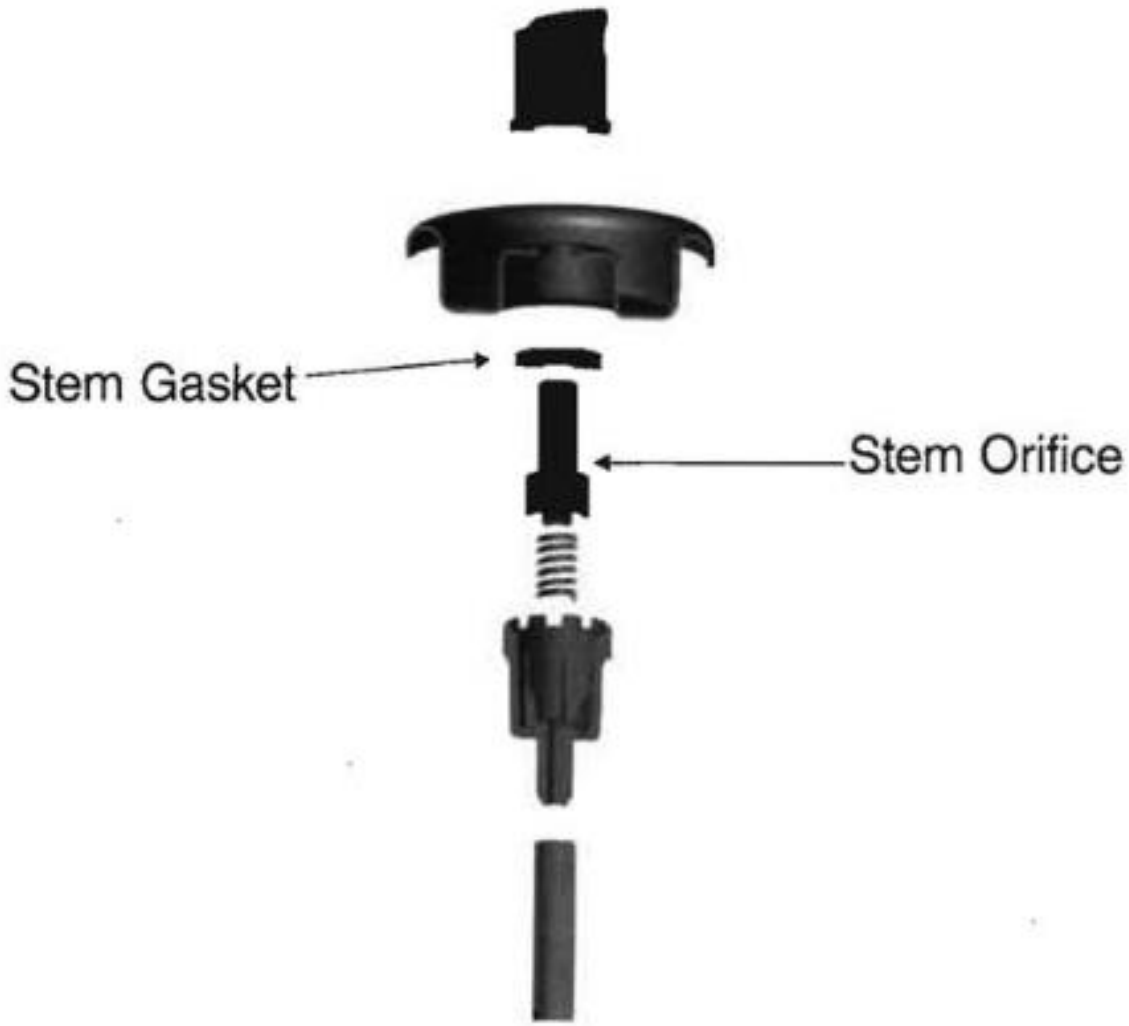
5. Housing

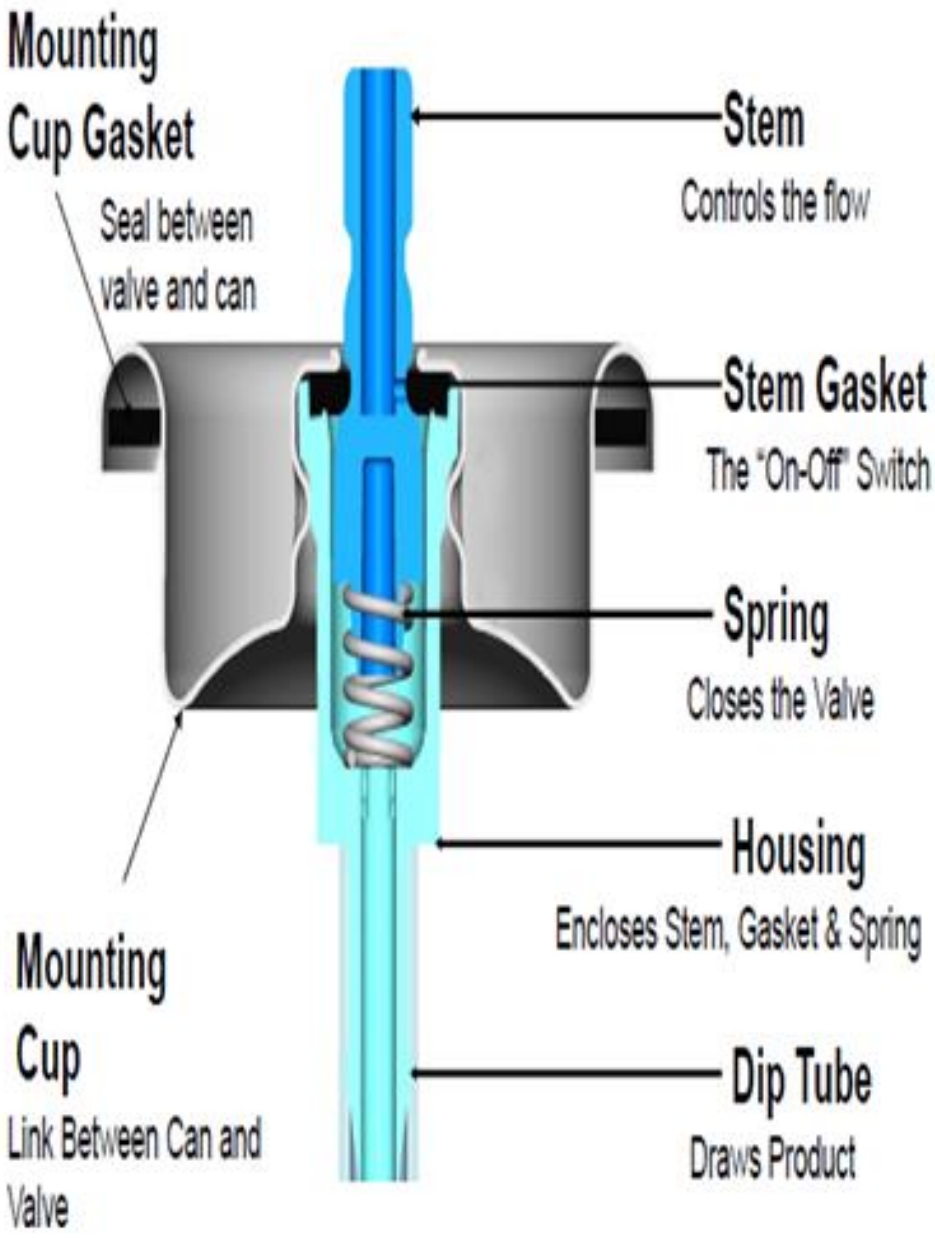
- Located directly below the mounting cup, it links the dip tube and the stem and actuator.

6. Dip tube

- Extends from the housing down into the product; brings the formulation from the container to the valve.

Cap
Actuator
Valve
Container


Stem Gasket
Stem Orifice


Mounting
Cup Gasket
Seal between
valve and can
Stem
Controls the flow
Stem Gasket
The "On-Off" Switch
Spring
Closes the Valve
Housing
Encloses Stem, Gasket & Spring
Mounting
Cup
Link Between Can and
Valve
Dip Tube
Draws Product

Actuators

- Specially designed button placed on the valve system which helps in easy opening and closing of the valve.
- It helps in delivering the product in the desired form.
- Different type of actuators are used: Spray Actuators, Foam Actuators, Solid Stream Actuators, Special Actuators.

- Spray actuator
  - The stream of product concentrate and propellant are dispensed in the form of small particle through orifices 0.016- 0.040inch.
  - Large orifice are used when high pressure of propellant.
- Foam Actuator:
  - They contain large orifice diameter 0.070-0.125 inch

- Semisolid stream actuator:
  - It is used for dispensing semisolid dosage form
- Special actuator:
  - They are specially designed to deliver the medicament on the specific sites like nose and throat

Aerosol formulation

- Aerosols contains two essential components:
  - **Product concentrate**
    - Contains ingredients or mixture of active ingredients and other such as solvents, antioxidants and surfactants
  - **Propellant**
    - Propellant may be single or blend of various propellants

- Classification of aerosols
  - According to administration route
    - Inhalation aerosols
    - Non-inhalation aerosols
    - Topical aerosols
  - According to the working way of valve
    - Metered dose aerosols
    - Non-metered dose aerosols

- According to dispersion system
  - Solution aerosol
  - Emulsion aerosol
  - Suspension aerosol
- According to the number of phases
  - Two phases aerosols
  - Three phases aerosols

- Four types of aerosol systems:
  - Solution system (Two phase system)
  - Water based system (Three phase system)
  - Suspension or Dispersion system
  - Foam system

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- **Solution system**
  - It is known as two-phase system since it consists of product concentrate and propellant.
  - The amount of propellant varies 5%(foams) to 95%(for inhalation purpose).
  - They are useful for inhalational preparation

- **Water based systems**
  - Three phase system consists of:
    - A layer of water- immiscible liquid propellant
    - A layer of highly aqueous product concentrate
    - A vapor phase
  - Ethanol is used as co-solvent in these systems to solubilize propellant in water
  - Surfactants (0.5-2%) are added for homogenous dispersion.

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- Stable foam
  - If the propellant is in the internal phase……..O (Liquefied propellant) /W emulsion……foam is emitted
  - Both hydrocarbons and compressed gas propellants may be used.
- Quick breaking foam
  - If the product concentrate is dispersed throughout the propellant ……..W/O emulsion……the product is dispersed as wet stream

- **Suspension or Dispersion system**
  - Active ingredients are suspended or dispersed throughout the propellant or propellant and solvent phase.
  - Problems associated with the formulation: Agglomeration, Caking, Particle-size growth and Valve clogging.
  - To overcome these problems:
    - **Lubricants:** Provide slippage between particles &/or Lubricate components parts of the valve
    - **Surfactants:** to disperse particles

Manufacturing of Pharmaceutical Aerosol

- The aerosol concentrate is first prepared and filled into the container.
- The propellant is then filled into the container.
- The filling operation measures to ensure that both concentrate and propellant are brought together in the proper proportion.

- Types of aerosol filling
  - Cold filling
  - Pressure filling
  - Compressed gas filling

Cold Filling Apparatus

- The principle of cold filling method requires the chilling of all components including concentrate and propellant to temperature of 0 to -40 ºF.
- The cooling system may be a mixture of dry ice and acetone or refrigeration system.
- The product concentrate is chilled and filled into already chilled container followed by the chilled liquefied propellant.

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- The heavy vapor of the cold liquid propellant generally displace the air in the container.
  - The valve is crimped in place.
  - The container is passed into a water bath (55 ºC) to ensure there is no leakage or distortion in the container.
- Limitations
  - Aqueous products, emulsions and those products adversely affected by cold temperature cannot be filled by this method.
  - For non-aqueous systems, some moisture usually appear in the final product due to condensation of atmospheric pressure

Pressure filling

- Pressure filling is carried out at room temperature under high pressure.
  - The concentrate may be chilled slightly (15-20 ºC) to reduce vaporization of any volatile solvent or propellant.
  - The concentrate is added to an open container
  - The valve is crimped in place
  - The propellant is added under pressure through the valve.

- Advantages
  - It is the preferred method for solutions, emulsions and suspension.
  - Less chances for contamination of product with the moisture.
  - Less propellant is lost.
  - No refrigeration is required, can be carried out at room temperature.

Compressed Gas Filling

- Compressed gases are present under high pressure in cylinders.
  - These cylinders are fitted with a pressure reducing valve and a delivery gauge.
  - The concentrate is placed in the container.
  - The valve is crimped in place.

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- Air is evacuated by means of vacuum pump.
- The filling head is inserted into the valve opening, valve depressed and gas is allowed to flow into the container.
- For those products requiring an increased amount of gas or those in which the solubility of gas in the product is necessary, carbon dioxide and nitrous oxide can be used.
- To obtain maximum solubility of the gas in the product, the container is shaken manually during and after the filling operation by mechanical shakers.

Evaluation of Aerosols

1. Flammability and Combustibility

- Flame Projection
  - This test indicates the effect of an aerosol formulation on the extension of an open flame.
  - Product is sprayed for 4 seconds into flame.
  - Depending on the nature of formulation, the flame is extended, and exact length was measured with ruler.

- Flash point
  - Determined by using standard Tag Open Cap Apparatus.
  - Aerosol product is chilled to temperature of –25ºF and transferred to the test apparatus.
  - Temperature of test liquid increased slowly, and the temperature at which the vapors ignite is taken a flash point.
  - Calculated for flammable component, e.g. topical hydrocarbons.

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2. Physiochemical characteristics

- Vapor pressure - Determined by pressure gauge
- Density - Determined by hydrometer or a pychnometer.
- Moisture content - By Karl Fischer method
- Identification of propellants - I.R spectrophotometer

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3. Performance

a) Aerosol valve discharge rate

- Determined by taking an aerosol known weight and discharging the contents for given time using standard apparatus.

- By reweighing the container after time limit has expired, the change in weight per time dispensed is **discharge rate**, expressed as gram per seconds.

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b) Dose uniformity

- To determine amount of medication actually received by the patient.
- The method involves accurate weighing of filled container followed by dispersing of several doses.
- Container can reweighed.
- Difference in weight divided by number of doses, gives the average dosage.

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c) Net contents

- Weight filled full container
- Dispensing the contents, then reweight the container (weight of empty container)
- The difference in weight, will be the net weight

d) Leakage

- Used to estimate the weight loss over a 1-year period.

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4. Particle size distribution

- By using Cascade Impactor
- Carrying particles in a stream of air through a series of consecutively smaller jet openings.
- The heavier and larger diameter particles are impacted on a slide under the larger opening.
- As the openings get smaller, the velocity of the stream increases and the next larger particles are deposited on the next slides.